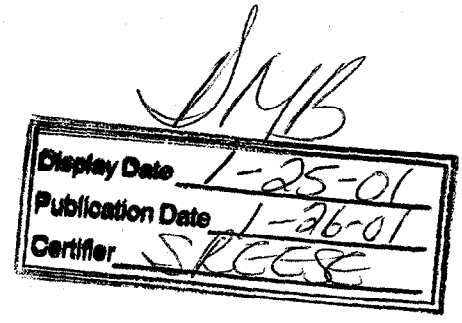
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration



21 CFR Part 201

[Docket No. 90N–0056]

RIN 0910–AA74

Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition; Delay of Effective Date

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; delay of effective date.

SUMMARY: The Food and Drug Administration (FDA) is delaying until January 26, 2003, the effective date of a final rule published in the **Federal Register** of January 26, 2000 (65 FR 4103), and originally scheduled to become effective on January 26, 2001. The final rule amends FDA's regulations to add certain labeling requirements for aluminum content in large volume parenterals (LVP's), small volume parenterals (SVP's), and pharmacy bulk packages (PBP's) used in total parenteral nutrition (TPN). The rule also specifies an upper limit of aluminum permitted in LVP's and requires applicants to submit to FDA validated assay methods for determining aluminum content in parenteral drug products. FDA is delaying the effective date of this rule to address concerns raised by affected parties about the possible inability to meet the requirements of the rule by the current effective date.

DATES: The effective date for § 201.323 (21 CFR 201.323), added at 65 FR 4103, January 26, 2000, is delayed until January 26, 2003. Submit written comments by [*insert date 90 days after date of publication in the* **Federal Register**].

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ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

On January 26, 2000, the agency published final regulations at § 201.323 (21 CFR 201.323) enacting certain requirements regarding aluminum levels in SVP's, LVP's, and PBP's used in TPN. The new regulations added to part 201 (21 CFR part 201) at § 201.323(a) limit the aluminum content for all LVP's used in TPN therapy to 25 micrograms per liter (µg/L). This requirement applies to all LVP's used in TPN therapy, including, but not limited to, parenteral amino acid solutions, highly concentrated dextrose solutions, parenteral lipid emulsions, saline and electrolyte solutions, and sterile water for injection.

New § 201.323(b) requires the package insert for all LVP's used in TPN therapy to state that the drug product contains no more than 25 µg/L of aluminum. This statement must be included in the ''Precautions'' section of the labeling.

New § 201.323(c) requires the product's maximum level of aluminum at expiry to be stated on the immediate container label of SVP's and PBP's used in the preparation of TPN solutions. The statement on the immediate container label must read as follows: ''Contains more than ____ µg/L of aluminum.'' For those SVP's and PBP's that are lyophilized powders used in the preparation of TPN solutions, the maximum level of aluminum at expiry must be printed on the immediate container label as follows: ''When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than ____ µg/L.'' The maximum level of aluminum must be stated as the highest of: (1) The highest level for the batches produced

during the last 3 years; (2) the highest level for the latest five batches, or (3) the maximum historical level, but only until completion of production of the first five batches after the effective date of the rule. The labeling requirement applies to all SVP's and PBP's used in the preparation of TPN solutions, including, but not limited to: Parenteral electrolyte solutions, such as calcium chloride, calcium gluceptate, calcium gluconate, magnesium sulfate, potassium acetate, potassium chloride, potassium phosphate, sodium acetate, sodium lactate, and sodium phosphate; multiple electrolyte additive solutions; parenteral multivitamin solutions; single-entity parenteral vitamin solutions, such as vitamin K injection, folic acid, cyanocobalamin, and thiamine; and trace mineral solutions, such as chromium, copper, iron, manganese, selenium, and zinc.

New § 201.323(d) requires the package insert for all LVP's, SVP's, and PBP's used in TPN to contain a warning statement. The warning statement must be included in the ''Warnings'' section of the labeling. The warning must contain the following language:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

New § 201.323(e) requires applicants and manufacturers to use validated assay methods to determine the aluminum content in parenteral drug products used in TPN therapy. The assay methods must comply with current good manufacturing practice regulations under part 211 (21 CFR part 211) (see § 211.194(a)). Holders of approved applications for LVP's, SVP's, and PBP's used in TPN therapy are required to submit a supplement to FDA under 21 CFR 314.70(c); see also 21 U.S.C. 356a(b) describing the assay method used for determining the aluminum content.

Applicants must submit the validation method used and the release data for several batches. In addition, manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections (see §§ 211.160 and 211.180(c)).

New § 201.323 applies to all human drug LVP's, SVP's, and PBP's used in TPN. Licensed biological products are not covered by this rule.

II. Description and Rationale for a Delay of the Effective Date of the Final Rule

Since publication of the final rule, the agency has received letters and has had other communications with industry and industry trade associations in which industry has stated the need for additional time to meet the requirements of the rule. In early June 2000, the agency met with representatives from industry and an industry association. The meeting participants discussed their concerns with the following issues: (1) Inadequate time for final rule implementation; (2) insufficient space on immediate container label of SVP's to state aluminum levels; (3) LVP's that will not meet the 25 µg/L limit without reformulation or repackaging; (4) unavailability of release data required for submission for low production products; (5) labeling SVP's and PBP's with less than 25 µg/L of aluminum; (6) the need for a uniform approach to aluminum testing during stability studies so that the sampling time points for the tests are the same for all products; and (7) clarification that the final rule applies only to LVP, SVP, and PBP drug products used in TPN and not to devices.

Industry and the industry association stated at this meeting that additional time is necessary for moving methods validation from research and development to production, to order and install equipment, and to reduce aluminum levels in raw materials. They also noted that a number of LVP's are in the 50 µg/L of aluminum range rather than the 25 µg/L range; therefore, these products will require repackaging or reformulation to meet the limit.

FDA has included in docket number 90N–0056 a copy of the meeting minutes. As part of the meeting, FDA confirmed the following: (1) That submission of historical batch release or stability data after completion of production of several batches is consistent with the final rule

as it exists; (2) that stability testing at time zero and annually thereafter is consistent with the final rule as it exists; (3) that the final rule applies only to LVP, SVP, and PBP drugs used in TPN; and (4) that when a PBP is divided into aliquots of LVP's, the LVP aliquots must meet the 25 µg/L aluminum limit required for all LVP's.

After the meeting, FDA confirmed that § 201.10(i) permits a small package exemption that applies to SVP's with insufficient space on the immediate container label to state aluminum levels.

FDA is issuing this notice to delay the effective date of the rule to address the concerns raised by industry regarding the inability to meet certain requirements of the rule within 1 year.

III. Comment on the Extension of the Effective Date

FDA placed minutes from the meeting described in Section II of this document in Docket No. 90N–0056 shortly after the meeting in June 2000. Those minutes and the memoranda of associated telephone calls set forth in detail the reasons a stay of the effective date for the aluminum rule until January 26, 2003, would be in the public interest. In particular, the agency is concerned that some products unable to reformulate by the existing effective date are medically necessary and without alternatives thus potentially putting certain patients at great risk. Since the agency is extending the effective date of the aluminum final rule based on the information submitted to it and the safety concerns associated with the potential unavailability of certain medically necessary products it finds, for good cause, that this extension of the effective date of the final rule does not require further notice and comment procedures (5 U.S.C. 553(b); 21 CFR 10.40(e)(1)). More than 6 months have passed since the agency placed supporting information in Docket No. 90N–0056, and the agency has received no adverse correspondence or comments with respect to the request to delay the extension date. In addition, FDA has received several telephone inquiries from other affected parties requesting a delay of the effective date. Therefore, the agency is now extending the effective date

of the final rule. However, in accordance with 21 CFR 10.40(e)(1), the agency will accept comment on this extension for a period of 90 days.

Dated: ~~January 16, 2001~~
January 18, 2001.

Ann M. Witt,
Acting Associate Commissioner for Policy.

[FR Doc. 01–???? Filed ??–??–01; 8:45 am]

BILLING CODE 4160–01–F